REMARKS/ARGUMENTS

With this amendment, claims 1, 15-17, 20, 24-25 and 28-31 are pending. Claims 2-14, 19, 21-23 and 26 are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in a January 17, 2006, Office Action.

I. Status of the claims

Claim 1 is amended to recite an HIV infection caused by a macrophage tropic-strain of HIV. Support for this amendment is found throughout the specification, for example, at page 1, lines 17-28. New claim 32 is the method of claim 1 but specifically recites a stem cell-rich population of cells that is umbilical cord blood. Support for this amendment is found throughout the specification, for example, at page 9, lines 20-22. New claims 33 and 34 depend from claims 1 and 32 and recite that multiple samples of stem cell-rich populations of cells are transplanted into the patient and that the multiple samples can be HLA unmatched. Support for these amendments is found throughout the specification, for example, at Figure 1. These amendments add no new matter.

II. Rejection for obviousness-type double patenting

Claims 1, 15-18, 20, 24-25 and 27-31 are provisionally rejected for alleged obviousness type double patenting over claims 1-35 of co-pending US Application No. 10/498,450. Applicants will file terminal disclaimers to overcome these rejections, if appropriate, when the claims are deemed otherwise allowable.

III. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 15-18, 20, 24-25 and 27-31 are rejected under 35 U.S.C. §112, first paragraph because allegedly, the specification does not provide enablement for one of skill to make and use an invention commensurate in scope with those claims, *i.e.*, methods to prevent or treat HIV by transplanting a stem-cell rich population of cells that carry a beneficial gene into the HIV patient. The Office Action also alleges that undue experimentation is required to practice

the claimed invention. To the extent the rejection applies to the claims as amended, Applicants respectfully traverse the rejection.

In order to establish a prima facie case of lack of enablement, the Examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Examiner has not provided any reason why those of skill would not be able to practice the claimed methods based on the disclosure of the specification and on information that was publicly available at the time of filing.

The Office Action in large part alleges that undue experimentation is required to practice the invention. As set forth in the Manual of Patent Examining Procedure (MPEP) §2164.01, "the test of enablement is not whether any experimentation is necessary, but whether... it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971). Moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

A. Scope of the claims

According to the Office Action at page 7, the scope of the claims requires undue experimentation form those of skill in order to practice the claimed invention. The Office Action described the claims as covering a method of treating or preventing infection by any HIV strain by transplanting any stem cell rich population of cells into an infected patient. In order to expedite prosecution, claim 1 is now amended to recite a method of treating an HIV infection caused by a macrophage tropic strain of HIV.

B. Requirement for reduction to practice

According to the Office Action at page 8, the invention was not reduced to practice at the time of filing and reduction to practice is required to meet the enablement standard. Applicants respectfully traverse this rejection. A working example is not required to meet the enablement requirement.

The MPEP at §2164.2 states that compliance with the enablement requirement "does not turn on whether an example is disclosed." The same MPEP section also clearly states that examples, if present, can be working or prophetic. Further, the specification need not contain an example if the invention is otherwise disclosed to allow one of skill to practice the invention without undue experimentation. MPEP §2164.2 *citing In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970). As described herein, the amended claims can be practiced by those of skill without undue experimentation.

C. Dosage of stem cells comprising a beneficial gene

According to the Office Action the claimed methods are not enabled because the specification allegedly does not teach how many stem cells can be used to confer resistance to HIV in an infected patient as compared to preventive treatment of a healthy individual. Office Action at page 8. The specification also alleges that the specification does not disclose the number of transplanted stem cells need to elicit a specific protective response. Applicants respectfully traverse this rejection.

According to the MPEP, it is not necessary to specify the dosage if it is known to one of skill that the information could be obtained without undue experimentation. For example, the enablement requirement would be met if one of skill, based on knowledge of compounds having similar physiological or biological activity, could practice the invention without undue experimentation. MPEP §2164.01(c). As discussed below, at the time of filing those of skill had knowledge of how and how many cells from, *e.g.*, a stem cell-rich population of cells, such as umbilical cord blood, to transplant into a patient, including a patient infected with a macrophage tropic strain of HIV or for prophylactic treatment of HIV.

The amended claims are directed to transplantation of an appropriate source of hematopoietic stem cells, *i.e.*, umbilical cord blood, into a person who has HIV or is at risk of developing HIV. Hematopoietic stem cell transplantation has been practiced by those of skill since the early 1960s mainly to treat hematalogic and lymphoid cancers and certain diseases of blood cells. Briefly, the patient's own hematopietic stem cell population is eliminated or reduced using techniques routinely practiced by those of skill, *e.g.*, radiation or chemotherapy. The patient is then transplanted with a source of hematopoietic stem cells, *e.g.*, from bone marrow, peripheral blood, or umbilical cord blood as claimed. Applicants submit as Exhibit A, a declaration from Dr. Robert Chow and Dr. Lawrence Petz describing the knowledge of umbilical cord blood transplants at the time of filing. According to Drs. Chow and Petz, nucleated cells and/or CD34+ cells are used as surrogates for the number of stem cells in an umbilical cord blood sample. The total number of stem cells used in a transplantation procedure is based on the weight of the patient, *e.g.*, nucleated cells and/or CD34+ cells per kilogram. Thus, the particular disease treated by hematopoietic transplantation does not determine the dosage of stem cells used for treatment. Rather, the deciding factor is the size (weight) of the patient. The Office Action does not provide any reasoning to indicate that those of skill are unable to determine patient weight and number of nucleated cells and/or CD34+ cells in a source of hematopoietic stem cells, *e.g.*, umbilical cord blood, without using undue experimentation. Therefore, the method of transplanting stem cell-rich populations of cells, *e.g.*, umbilical cord blood cells, into a patient infected with HIV or for prophylactic treatment of HIV is enabled.

Applicants present as Exhibit B, an abstract entitled "Hematopioetic Stem Cell Transplantation (HSCT) using Umbilical Cord Blood Units (UCB) Not Depleted of Red Blood Cells Prior to Cryopreservation" co-authored by some of the inventors. The abstract presents data that both adult and pediatric patients were successfully transplanted with UCB after elimination of the patient's own hematopoietic cells. The data also indicates that a single cord blood unit is sufficient for transplantation of many patients and that, with appropriately matched HLA markers, two cord blood units can be used to transplant larger patients. Thus, expansion of a stem cell population from a stem cell source is not required to successfully transplant a patient

using umbilical cord blood as a stem source. The Office Action has not provided any convincing reasoning to suggest that expansion of stem cells is required to practice the claimed invention.

D. Individuals that carry beneficial genes can be identified in human populations

According to the Office Action the claimed methods are not enabled because the art shows that beneficial genes are not uniformly present in the human population and, that in order to practice the claimed methods, unpredictable *ex vivo* or *in vitro* methods must be used to expand a population of stem cells from a stem cell source before transplantation. Office Action at page 9. Applicants respectfully traverse this rejection.

As described above, expansion of a population of stem cells before transplantation is not required to practice the claimed invention and the Office Action does not present any reasoning to suggest otherwise. Moreover, the specification at Examples 1 and 2 on page 13, provides the first disclosure of screening multiple cord blood samples to identify a source of stem cells that has a beneficial gene. Applicants present as Exhibit C, WO/2003/045335, a related PCT publication that discloses actual reduction to practice of the collection of stem cell sources from multiple unrelated cord blood donors. At paragraph 78, WO/2003/045335 discloses results of screening about five thousand umbilical cord samples from unrelated donors. Twenty two samples with homozygous CCR5 delta 32 polymorphisms were identified and about 500 samples with heterozygous CCR5 delta 32 polymorphisms were identified. Thus, Applicants are the first to demonstrate that sources of stem cells with beneficial genes, *e.g.*, umbilical cord blood, can be identified and collected for use in the claimed methods. This demonstration also provides evidence that allegedly unpredictable *ex vivo* or *in vitro* methods to expand stem cell populations are not required to practice the claimed invention. Thus, the specification teaches how to obtain a stem cell-rich population of cells for transplantation, *e.g.*, umbilical cord blood cells, and how to transplant the cells into a patient. Therefore, the claimed methods are enabled.

E. Roman et al. confirm earlier findings and do not present contradictory data.

According to the Office Action, Roman *et al.*, a reference cited by the Examiner, provides contradictory evidence that in certain circumstances a CCR5 polymorphism did not provide resistance to HIV infection. Office Action at page 10. Applicants respectfully disagree with this interpretation of Roman *et al.*

The Office Action discusses a paragraph that begins at page 195 right column and continues to page 196. In fact this paragraph discloses that two polymorphisms previously thought to be distinct, were actually the same. Roman *et al.* first state that an HIV-1 A/G polymorphism at position 59029 had been identified and that the individuals with the G/G genotype (59029-G) had delayed onset of AIDS when compared to individuals with the A/A genotype (59029-A). In other words, the A/A phenotype had increased onset to AIDS as compared to the G/G genotype. Roman then describe a homozygous CCR5 promoter variant, CCR5-P1, that has accelerated onset of AIDS. Roman *et al.* then state that CCR5-P1 and 59029-A genotypes, both having increase or accelerated onset of AIDS, appear to be the same. Thus, Roman *et al.* do not disclose contradictory results. Roman *et al.* go on to analyze the incidence of CCR5 polymorphisms in Luxembourg and conclude that the distribution of the polymorphisms is the same in the Luxembourg population as had been found previously in other Caucasian populations. Therefore, Roman *et al.* cannot be used to argue lack of enablement of the claimed invention.

F. Undue experimentation is not required to practice the claimed invention.

Applicants recognized that hematopoietic stem cells with naturally occurring beneficial genes could be used to replace the circulating immune system of patients with HIV infection or people who are likely to become infected with HIV. Applicants further demonstrated that donors of a source of hematopoietic stem cells with naturally occurring beneficial genes, *e.g.*, umbilical cord blood, could be identified from the population. The techniques used for hematopoietic stem cell transplantation from a variety of sources are well known, *e.g.*, umbilical cord blood, bone marrow, and peripheral blood. The treatment of a variety of diseases using hematopoietic stem cell transplantation has been demonstrated.

Treatable diseases include malignancies and genetic disorders, *e.g.*, thalassemia. The Office Action has not provided any reasoning to suggest that those of skill would not be able to eliminate the endogenous immune system and then reconstitute by hematopoietic stem cell transplantation a new immune system of a patient with an HIV infection or a person likely to become infected with HIV as is done for other diseases. Absent such reasoning, arguments related to the alleged requirement for undue experimentation cannot be maintained.

CCR5 beneficial mutations were identified in persons infected with HIV for long periods before onset of AIDS or who appeared to not develop AIDS. As indicated above, those of skill are able to eliminate the immune cells of a patient with a lymphoma or with thalassemia and replace those cells with donor cells that have a more desirable phenotype, thereby providing treatment for the patient. The Office Action has not provided any reasoning to suggest that those of skill would not be able to eliminate the endogenous immune system of a patient infected with a macrophage tropic-strain of HIV or a person likely to become infected with such a strain and then reconstitute by hematopoietic stem cell transplantation of cells with a beneficial gene that would delay the onset AIDS. Onset of AIDS has been delayed or halted in individuals who carry beneficial genes naturally and who are infected with, *e.g.*, a macrophage tropic HIV strain. The language of the claims does not require a cure of HIV infection. Any delay in AIDS onset is efficacious and provides a treatment for HIV infected patients. The Office Action has not provided any reasoning to suggest that claimed umbilical cord blood transplants would be without effect on the time to onset of AIDS following HIV infection. Absent such reasoning, arguments related to the alleged requirement for undue experimentation cannot be maintained.

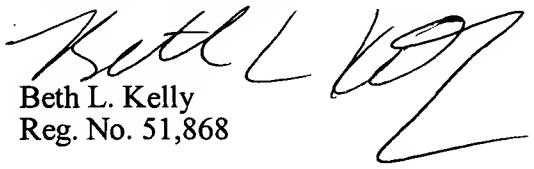
In view of the above arguments and amendments, withdrawal of the rejection for alleged lack of enablement is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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